SIDE EFFECTS OF AMIODARONE/Harris et al. 45


Side Effects of Long-term Amiodarone Therapy
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SUMMARY Although amiodarone is an effective antiarrhythmic agent, long-term therapy may be associated with unwanted effects. We report our experience in 140 patients treated over 5 years. Important effects were seen particularly in the thyroid gland, liver, lung and skin. Some of these effects are dose-dependent and others may be related to the chemical structure and metabolism of amiodarone. Corneal microdeposits were always found when sought, but did not cause impairment of visual acuity.

AMIODARONE has been available in Europe for approximately 20 years for the management of angina pectoris,1 but only in the past decade have its unique antiarrhythmic properties been recognized.2 It is effective in the management of refractory ventricular arrhythmias, including those associated with ischemic heart disease and the cardiomyopathies.3,4 It is particularly useful in the management of chronic atrial arrhythmias refractory to conventional drugs, with an impressive conversion rate of chronic atrial fibrillation to sinus rhythm.4 Amiodarone is especially effective in suppressing or modifying paroxysmal atrial arrhythmias, including those associated with the Wolff-Parkinson-White syndrome,5 in which sudden death from rapidly conducted atrial fibrillation is a risk.6

With the more widespread use of amiodarone, several side effects have been identified. In the majority of patients, these are well tolerated and are often modified by a reduction in dosage so that discontinuation of therapy is rarely necessary. A few patients, however, have more serious complications, including pulmonary fibrosis7,8 and clinical thyroid disease.9 The incidence, mechanisms and management of these complications is uncertain. Our experience in individual cases dates back over 9 years. We are now able to report 140 patients in whom we have systematically monitored the unwanted effects over the past 5 years.

Patients and Dosage
We reviewed 140 patients (95 males and 45 females, mean age 52 years) who had been taking amiodarone for an average of 2 years; the longest follow-up was 5 years. Although 69 of our patients were taking amiodarone for primary arrhythmias, including the Wolff-Parkinson-White syndrome, we also treated 15 patients with ischemic heart disease and 48 who had arrhythmias associated with cardiomyopathy, 28 hypertrophic and 20 congestive. Five patients had valvular disease, two hypertensive heart disease and one patient an atrial septal defect. Details of the arrhythmias treated are listed in table 1.

The dose varied from 100 to 1200 mg/day, but only 11 patients took 600 mg/day or more long-term; the
TABLE 1. Arrhythmias Treated with Amiodarone

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>No. of pts</th>
<th>Mean dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular tachycardia</td>
<td>46</td>
<td>440 (200-1200)</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
<td>10</td>
<td>490 (200-600)</td>
</tr>
<tr>
<td>Chronic atrial fibrillation/flutter</td>
<td>15</td>
<td>310 (200-400)</td>
</tr>
<tr>
<td>Paroxysmal atrial arrhythmia</td>
<td>38</td>
<td>280 (100-400)</td>
</tr>
<tr>
<td>Supraventricular arrhythmias, including Wolff-Parkinson-White syndrome</td>
<td>31</td>
<td>350 (100-600)</td>
</tr>
</tbody>
</table>

The unwanted effects are categorized as thyroid, hepatic, pulmonary and cutaneous. Ocular and neurologic changes are also considered, as are alterations in cardiac conduction and repolarization.

Thyroid

Changes in thyroid function were recognized early,9,12 the most common was a rise in thyroxine (T4) and reverse triiodothyronine (rT3) levels, and a fall in triiodothyronine (T3).13 There is also an associated incidence of clinical thyroid disease.

We measured T4 in 10 patients and rT3 in nine of the same 10 patients systematically over an 18-month period. All had normal thyroid function at the start of treatment (fig. 1). T4 decreased in the first 2 weeks of treatment in four of the patients, but thereafter levels increased in all; rT3 increased in all subjects (increase of 79% over 18 months). In addition to these detailed serial observations, we measured T4 in 85 additional patients. The mean T4 level for the group was elevated by 20% above the mean for the laboratory (fig. 2). In five, the T4 level decreased and thyroid-stimulating hormone (TSH) increased (table 2); two of these patients were clinically myxedematous. In contrast, four patients had increased T4 levels of 25% or more above the upper limit of normal (table 2); two were clinically thyrotoxic. To identify predisposing factors in these patients with marked alterations in thyroid function,
we examined various clinical features. All had normal thyroid function before treatment, and none developed goiter. There was no family history of thyroid disease, and thyroid antibody titers were negative in all. The mean duration of treatment before changes were observed was 30 months, and all but two patients were receiving moderate doses, with appropriate plasma drug concentrations.\textsuperscript{14} Of the five hypothyroid patients, four were more than 70 years old. Generally, TSH does not increase in relation to age in men.\textsuperscript{15} However, four of the five patients were male, suggesting that there may be an increased risk of thyroid dysfunction in older patients taking amiodarone, irrespective of their sex. Treatment was discontinued in one patient (table 2), but T4 was added after 6 weeks because clinical hypothyroidism persisted. In another patient (table 2), treatment could not be discontinued because of the intractability of the arrhythmia; therefore, amiodarone was continued and T4 replacement initiated. Both patients are now clinically and biochemically euthyroid on replacement T4.

More difficult to assess, and more insidious in presentation, is increased thyroid activity on amiodarone. As the majority of patients have some elevation of T4 on chronic therapy and some may have tremor and sleep disturbance, the diagnosis of thyrotoxicosis may be difficult. In our two clinically thyrotoxic patients, the diagnosis rested on raised T3 levels (4 nmol/l and 5.3 nmol/l respectively), increasing weight loss, anxiety and weakness. Response to thyrotropin-releasing hormone (TRH) was not measured, but a flattened response would have assisted in the diagnosis. There was no recurrence of the underlying arrhythmia in either patient. Thyrotoxicosis resolved spontaneously, as judged biochemically and clinically, in both patients 1–2 months after treatment was stopped.

Several mechanisms have been proposed to explain this spectrum of altered thyroid activity. Amiodarone does not interfere in the T4 assay and does not modify the T4-binding globulin concentration.\textsuperscript{12, 13} Each 200-mg tablet of amiodarone contains approximately 75 mg of organic iodine and, in the steady state, metabolism of 300 mg of amiodarone yields 9 mg/day of iodine,\textsuperscript{16} which represents a 100-fold increase over the normal iodine intake. The effects of a chronic iodine load on thyroid function have been well documented and both iodine-induced hypothyroidism\textsuperscript{17} and hyperthyroidism\textsuperscript{18} can occur in apparently normal glands. An additional acute antithyroid action of an iodine

![Thyroxine levels in 95 patients during treatment with amiodarone. The mean level was 124 nmol/l (mean for normal persons 102 nmol/l).](image)

### Table 2. Patients with Gross Alterations in Thyroid Function Tests on Amiodarone

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Arrhythmia</th>
<th>Dose (mg/day)</th>
<th>Duration (months)</th>
<th>T4 (nmol/l) on amiodarone</th>
<th>Free T4 (pmol/l)</th>
<th>TSH (mg/l)</th>
<th>Amiodarone (mg/l)</th>
<th>Desethyl amiodarone (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JE*</td>
<td>70</td>
<td>M</td>
<td>AFI</td>
<td>200</td>
<td>39</td>
<td>8</td>
<td>—</td>
<td>&gt;25</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>FD*</td>
<td>77</td>
<td>F</td>
<td>SND</td>
<td>200</td>
<td>10</td>
<td>33</td>
<td>—</td>
<td>&gt;60</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LH</td>
<td>76</td>
<td>M</td>
<td>AFI</td>
<td>200</td>
<td>29</td>
<td>44</td>
<td>—</td>
<td>&gt;20</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>RM</td>
<td>77</td>
<td>M</td>
<td>VT</td>
<td>200</td>
<td>36</td>
<td>24</td>
<td>—</td>
<td>19</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>MD</td>
<td>59</td>
<td>M</td>
<td>VT</td>
<td>600</td>
<td>32</td>
<td>25</td>
<td>—</td>
<td>&gt;25</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF†</td>
<td>48</td>
<td>M</td>
<td>VT</td>
<td>400</td>
<td>34</td>
<td>226</td>
<td>39.5</td>
<td>&lt;1</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>GF†</td>
<td>62</td>
<td>M</td>
<td>VT</td>
<td>400</td>
<td>32</td>
<td>207</td>
<td>42.0</td>
<td>&lt;1</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>AF</td>
<td>40</td>
<td>M</td>
<td>CAF/Fl</td>
<td>600</td>
<td>26</td>
<td>193</td>
<td>37</td>
<td>—</td>
<td>4.6</td>
<td>3.8</td>
</tr>
<tr>
<td>SB</td>
<td>18</td>
<td>F</td>
<td>SVT/WPW</td>
<td>400</td>
<td>36</td>
<td>231</td>
<td>67.2</td>
<td>—</td>
<td>0.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Normal range: thyroxine 45–160 nmol/l; free thyroxine 0.8–24 pmol/l.

*Clinically myxedematous.
†Clinically thyrotoxic.

Abbreviations: AFI = atrial flutter; SND = sinus node disease; VT = ventricular tachycardia; CAF/Fl = chronic atrial fibrillation/flutter; SVT = paroxysmal supraventricular tachycardia; WPW = Wolff-Parkinson-White syndrome; T4 = thyroxine; TSH = thyroid stimulating hormones.
load, the Wolff-Chaikoff effect,\textsuperscript{19} may explain the initial fall in T4 in some of our patients (fig. 2). In normal persons, as in our patients, this effect is transient even with continued iodine administration, because of autoregulatory inhibition of intrathyroid iodide transport. Amiodarone itself may have a direct action on the thyroid gland, but in vitro studies have shown no alteration of active iodide transport, iodine organification or iodotyrosine deiodination.\textsuperscript{20} However, a direct intrathyroid action in vivo cannot be ruled out if amiodarone is substantially concentrated in the gland. In a single postmortem observation of a patient not included in this series, concentrations of amiodarone and desethyl amiodarone of 15 mg/kg and 92 mg/kg, respectively, were found in the thyroid gland. Amiodarone is also reported to inhibit the peripheral conversion of T4 to T3 with increased conversion along the alternative pathway to rT3, resulting in a rise in T4 and rT3, with a low or normal T3\textsubscript{s}\textsuperscript{12} our findings are consistent with this suggestion.

**Hepatic**

Hepatic dysfunction from drugs is well recognized. The liver enzymes rise in patients on large doses of amiodarone, but clinically evident hepatic dysfunction has not been detected. In 15 of 100 patients taking amiodarone, we found a 1.5–4-fold increase in serum aspartate aminotransferase levels. These changes are seen in patients on high doses and correlate with plasma concentrations of amiodarone ($r = 0.59$, $p < 0.001$) and its desethyl metabolite ($r = 0.62$, $p < 0.001$) (fig. 3). There was a similar increase in alanine aminotransferase and a minimal increase in gamma glutamyl transeptidase, with no change in serum bilirubin or alkaline phosphatase. Other investigators have reported similar alterations in hepatic function. Heger et al.\textsuperscript{8} reported a twofold increase in aspartate aminotransferase and lactic dehydrogenase in about 50% of their patients and Plomteaux et al.\textsuperscript{21} reported increased levels of aspartate aminotransferase and malic dehydrogenase in 10–20% of 36 patients. These changes are not persistent and may fluctuate within the individual patient over time; they usually return to normal despite continued treatment. None of our patients or those in these two series\textsuperscript{8, 21} has developed clinical hepatic dysfunction. We performed liver biopsies in two patients who had increased enzyme levels, but no changes attributable to amiodarone could be demonstrated in either biopsy. In the one biopsy suitable for measurement, there were high concentrations of amiodarone (1020 mg/kg), and particularly, desethyl amiodarone (5050 mg/kg). Similar concentrations in hepatic tissue were found postmortem in a patient not reported in this series with ischemic heart disease who died suddenly. Although amiodarone is also metabolized in the liver, these high concentrations probably reflect large hepatic stores of the parent compound, and especially its metabolite.

Hepatic injury due to drugs is common, having both a wide variety of mechanisms and a wide spectrum of presentation. Furan derivatives can cause centrilobular hepatic necrosis in rats,\textsuperscript{22} and amiodarone or its metabolites may produce similar injury. The high incidence of dose-dependent hepatic changes with amiodarone suggests a toxic effect rather than host idiosyncrasy as the underlying mechanism. In our experience, the changes are transient and do not progress. We therefore monitor hepatic function regularly in patients with raised hepatic enzyme levels, but do not discontinue amiodarone.

**Pulmonary**

Amiodarone has recently been suggested as a possible, albeit rare, cause of pulmonary fibrosis. Only one of our patients developed pulmonary interstitial changes with an associated restrictive pattern on pulmonary function testing. Review of his radiographs, however, revealed that such changes may have been present before treatment. In addition, a Kveim test had been positive 4 years previously, but other evidence of sarcoidosis was lacking. To identify common predisposing factors, we reviewed the five additional cases that were previously reported.\textsuperscript{7, 8, 23} Three of the total of six patients had been in severe cardiac failure and four were on high doses (800 mg/day). The interval before the onset of changes varied widely (2–28 months). There were no other distinguishing clinical features. In our patient, immunoglobulin concentrations were elevated and antinuclear antibodies, previously negative, were positive at a titer of 1:200. These abnormalities were not detected in the one other patient\textsuperscript{21} in whom
they were sought. Lung biopsies were performed in four of the patients, but only nonspecific features — alveolar wall fibrosis and atypical pneumocytes — were demonstrated. In our patient and in three previously described, the pulmonary changes resolved after the amiodarone had been discontinued and corticosteroids commenced. None has been rechallenged with amiodarone. The two remaining patients died of severe coexistent heart failure.

The mechanism of pulmonary injury is unknown. Our patient had positive antinuclear antibodies and elevated immunoglobulin levels; one possibility is a drug-induced autoimmune disorder. No conclusions can be drawn, however, as these tests were normal in the one other patient in whom they were measured. Alternatively, a direct toxic effect may occur. The roles of high dosage and of cardiac failure must be explored.

**Amiodarone Dermatopathy**

Two types of skin reaction have been described. Photosensitivity is common, but there is also a rare slate-gray pigmentation of the exposed areas. Photosensitivity is the commonest side effect reported by our patients (57%). There is a wide spectrum of skin reaction, ranging from an increased propensity to suntan during the summer months to intense burning, erythema and swelling of the exposed areas. We reviewed dosage and measured plasma concentrations of amiodarone and its metabolite in patients with and without photosensitivity, but found no significant difference between the two groups. However, the intensity of the reaction can be alleviated by a reduction in dosage and most patients can be protected by prophylactic barrier creams. None of our patients had to stop treatment. We observed a different skin reaction in the first 2 weeks after starting amiodarone in six patients: a pruritic, erythematous, fine maculopapular rash with a predominantly truncal distribution. It resolved spontaneously within days and did not require treatment or cessation of therapy.

Two patients have developed a slate gray/purple pigmentation of the face (fig. 4). They had been taking 600 mg/day for 5 and 2 years, respectively, for control of ventricular arrhythmias. Although not excessive for the dosage they were receiving, both patients had high plasma concentrations of amiodarone (3.1 mg/l in both) and desethyl amiodarone (3.7 mg/l and 3.2 mg/l, respectively). In one of these patients, biopsies were taken from affected skin (forehead) and unaffected skin (forearm). Lipofuscin deposits were noted in both, but were more conspicuous in the affected skin. Intense elastic degeneration, inappropriate for the age and solar exposure of the patient, was seen in affected skin only. Surprisingly, melanin was reduced in the affected skin. Other investigators have also demonstrated increased lipofuscin deposits, both histologically and histochemically, in the cells of the dermis of similar patients and most attribute the pigmentation to this. Similar facial pigmentation (visage mauve) has been described with prolonged use of high doses of phenothiazine derivatives, such as chlorpromazine, which also causes photosensitivity.37 Similar histologic deposits have been thought to represent complexes of chlorpromazine or one of its metabolites. Methacycline — another agent causing photosensitivity28 — also causes intense elastic degeneration in the dermis.

Forty percent of the 34 pigmented patients reported with amiodarone24-26, 29-32 had been taking 600 mg/day for an average of 2 years before pigmentation developed; this is consistent with the pigmentation being dose-duration dependent. Furthermore, both of our patients, as well as almost all of those reported, had experienced photosensitivity before the development of pigmentation. Perhaps photosensitivity predisposes to elastic degeneration, with subsequent increased deposition of lipofuscin and skin discoloration in patients on high doses. If the pigmentation is cosmetically unsightly, amiodarone should be discontinued. In our one patient who discontinued it and in others, pigmentation improved over a period of 6–12 months. Our data suggest that this pigmentation can be avoided if doses are kept as low as possible.

**Ocular**

Deposits occur in the cornea with amiodarone. These deposits, detected on slit-lamp examination, have been widely described, but no other ocular changes have been reported.34, 35 We observed corneal deposits as early as 10 days after starting amiodarone, and they are present in all of our patients undergoing ophthalmologic examination after 1 month. These deposits occur peripherally in the cornea, and do not
produce symptoms. However, two of our patients using 600 mg/day complained of blue/green haloes on looking at bright lights and were found to have corneal deposits encroaching on the pupil. Both responded to a reduction in dosage. We have observed no other ophthalmologic complications, and no patient has required discontinuation of therapy for ocular side effects. Therefore, we no longer advise serial ophthalmologic examinations in asymptomatic patients on long-term amiodarone.

Neurologic
Peripheral neuropathy has been seen in rare instances with long-term amiodarone therapy, and intracellular inclusion bodies, similar to those seen in skin, have been demonstrated in peripheral nerve fibers. Proximal weakness, with predominant involvement of the thigh muscles, was observed in eight of our patients in the first weeks of therapy. It occurred in patients taking high doses (800 mg/day or more) and resolved spontaneously or with a reduction in dose. A delay in nerve conduction but normal electromyograms were demonstrated in two other patients taking 1800 and 2000 mg/day, respectively; both responded to a reduction in dosage.

Clinically distinct from this is the problem of peripheral neuropathy. There are several reports of a sensorimotor neuropathy, with a glove and stocking distribution, in patients using moderate (400 mg/day) to large doses (1800 mg/day) for 1 year or longer.36-39 Nerve conduction velocity is reduced. Histologically, segmental demyelination of the nerve fibers has been demonstrated as well as lipid-containing lysosomal inclusion bodies in the Schwann cells. Although the neuropathy resolves when treatment is discontinued, this is often slow and incomplete. Some of the patients described were using other drugs, including perhexiline, but in other cases there were no apparent predisposing factors. None of our patients developed this complication, and there does not appear to be a means of identifying which patients are at risk.

Cardiac Conduction and Repolarization
The electrophysiologic effects of amiodarone include depression of sinus40 and atrioventricular nodal function and prolongation of myocardial refractoriness,41 reflected in the surface ECG as a decrease in heart rate and repolarization changes.

Although amiodarone has been used safely in patients with the sick sinus syndrome,42 it does prolong sinus cycle length4 and sinus node recovery time.40 The concurrent administration of other antiarrhythmic drugs, such as β blockers, may result in sinus arrest.43 Amiodarone increases plasma digoxin concentrations,44 but the effect of this interaction on arrhythmias is uncertain. Prolongation of the QTc interval occurs in the majority of patients and is the electrocardiographic expression of the drug effect on the action potential duration. It does not appear to have the same implications as a similar degree of QTc prolongation seen with quinidine-like antiarrhythmic agents. McComb et al.45 suggested an association between amiodarone and atypical ventricular tachycardia. We do not agree that their patient had torsade de pointes,46 which has not occurred in any of our patients; nor had it been found when amiodarone was given as the sole agent in an extensive review of use of amiodarone in France.47

The mechanisms of the unwanted effects seen in patients receiving amiodarone fall into two broad groups. Some of the effects are dose-related. This is particularly clear in the elevation of the serum aminotransferases, where almost all patients who take 600 mg/day or more have raised levels. Other effects are both dose- and duration-dependent; the extent of the corneal microdeposits and the abnormal facial pigmentation are the best examples. These effects of long-term high doses make careful balance of dose against arrhythmia control imperative. In contrast, the effects on the thyroid gland and the peripheral nerves appear to be independent of these factors and suggest specific reactions in individual patients; thus, older patients on amiodarone appear to run an increased risk of myxedema. Until we have a better understanding of the mechanism of the pulmonary reaction, this effect cannot be defined.

Regardless of the mechanisms of these unwanted effects, almost all, with the possible exception of myxedema, resolve when treatment is discontinued. Amiodarone has proved sufficiently valuable for serious arrhythmias that its judicious administration is often required; its benefit will clearly be greatest when knowledge of its side effects is complete.

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